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CME

Assessment of Conventional Cardiovascular Risk Factors and Multiple Biomarkers for the Prediction of Incident Heart Failure and Atrial Fibrillation

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Assessment of Conventional Cardiovascular Risk Factors and Multiple Biomarkers for the Prediction of Incident Heart Failure and Atrial Fibrillation

Objectives The purpose of this study was to assess the predictive accuracy of conventional cardiovascular risk factors for incident heart failure and atrial fibrillation, and the added benefit of multiple biomarkers reflecting diverse pathophysiological pathways.

Background Heart failure and atrial fibrillation are interrelated cardiac diseases associated with substantial morbidity and mortality and increasing incidence. Data on prediction and prevention of these diseases in healthy individuals are limited.

Methods In 5,187 individuals from the community-based MDCS (Malmö Diet and Cancer Study), we studied the performance of conventional risk factors and 6 biomarkers including midregional pro-atrial natriuretic peptide (MR-proANP), N-terminal pro–B-type natriuretic peptide (NT-proBNP), midregional pro-adrenomedullin, cystatin C, C-reactive protein (CRP), and copeptin.

Results During a mean follow-up of 14 years, 112 individuals were diagnosed with heart failure and 284 individuals with atrial fibrillation. NT-proBNP (hazard ratio [HR]: 1.63 per SD, 95% confidence interval [CI]: 1.29 to 2.06, $p < 0.001$), CRP (HR: 1.57 per SD, 95% CI: 1.28 to 1.94, $p < 0.001$), and MR-proANP (HR: 1.26 per SD, 95% CI: 1.02 to 1.56, $p = 0.03$) predicted incident heart failure independently of conventional risk factors and other biomarkers. MR-proANP (HR: 1.62, 95% CI: 1.42 to 1.84, $p < 0.001$) and CRP (HR: 1.18, 95% CI: 1.03 to 1.34, $p = 0.01$) independently predicted atrial fibrillation. Addition of biomarkers to conventional risk factors improved *c*-statistics from 0.815 to 0.842 for heart failure and from 0.732 to 0.753 for atrial fibrillation and the integrated discrimination improvement for both diseases ($p < 0.001$). Net reclassification improvement (NRI) with biomarkers was observed in 22% of individuals for heart failure (NRI, $p < 0.001$) and in 7% for atrial fibrillation (NRI, $p = 0.06$), mainly due to up-classification of individuals who developed disease (heart failure: 29%, atrial fibrillation: 19%). Addition of CRP to natriuretic peptides did not improve discrimination or reclassification.

Conclusions Conventional cardiovascular risk factors predict incident heart failure and atrial fibrillation with reasonable accuracy in middle-age individuals free from disease. Natriuretic peptides, but not other biomarkers, improve discrimination modestly for both diseases above and beyond conventional risk factors and substantially improve risk classification for heart failure. (J Am Coll Cardiol 2010;56:1712–9) © 2010 by the American College of Cardiology Foundation

Although the incidence of coronary heart disease has declined in recent years, the incidence of heart failure and atrial fibrillation has risen (1). These interrelated diseases (2) are major causes of morbidity and mortality (3,4), with lifetime risks as high as 20% and 25%, respectively (5,6). Accordingly, practice guidelines for heart failure and atrial fibrillation have shifted their emphasis from treatment to prevention (7,8).

The identification of individuals at risk for heart failure and atrial fibrillation remains a challenge, however. Previous studies have identified risk factors for heart failure (9,10) and atrial fibrillation (11,12), and risk scores for risk assessment have been developed (13–15). However, these scores have focused on specific subgroups (elderly, patients with hypertension, coronary heart disease, or valvular heart disease) and require information on markers rarely used in the clinic today, such as radiologic evidence of cardiomegaly. Additionally, many individuals who develop heart failure and atrial fibrillation are not identified by risk factors, reflecting the etiologic heterogeneity of these diseases.

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Abbreviations and Acronyms

CRP = C-reactive protein
ICD = International Classification of Diseases
IDI = integrated discrimination improvement
MR-proADM = midregional pro-adrenomedullin
MR-proANP = midregional pro-atrial natriuretic peptide
NRI = net reclassification improvement
NT-proBNP = N-terminal pro–B-type natriuretic peptide
ROC = receiver-operating characteristic

Asymptomatic ventricular dysfunction frequently precedes heart failure or atrial fibrillation, but routine screening echocardiography is prohibitively expensive and not currently recommended in the general population. It has been suggested that biomarkers reflecting common pathophysiological processes (16) may perform better than standard risk factors and identify individuals who might benefit from echocardiographic screening. A number of plasma biomarkers have been related to heart failure (16) and atrial fibrillation risk (17,18). However, the predictive value of models incorporating multiple biomarkers together has not been well established.

In a population-based sample of middle-aged individuals, we sought to evaluate the predictive accuracy of conventional cardiovascular risk factors and the incremental predictive value of a panel of biomarkers reflecting diverse pathophysiological pathways implicated in heart failure and atrial fibrillation including *hemodynamic stress* (the midregional fragment of pro-atrial natriuretic peptides [MR-proANP], the amino-terminal fragment of pro–B-type natriuretic peptide [NT-proBNP], the midregional fragment of pro-adrenomedullin [MR-proADM]), *plasma volume and osmolarity* (copeptin), *inflammation* (C-reactive protein [CRP]), and *renal function* (cystatin C). We evaluated model improvement using both the c-statistic and the newer measures of integrated discrimination improvement (IDI) and net reclassification improvement (NRI) (19–21).

Methods

Study sample. The MDCS (Malmö Diet and Cancer Study) is a prospective cohort study that includes 28,449 men (born between 1923 and 1945) and women (born between 1923 and 1950) from the city of Malmö in southern Sweden who underwent baseline examinations between 1991 and 1996. From this cohort, 6,103 individuals with a baseline examination between 1991 and 1994 were randomly selected to participate in a study of cardiovascular risk factors, the MDCS Cardiovascular Cohort (MDC-CC), of whom 5,543 underwent blood sampling under standardized fasting conditions (22). Information on all conventional risk factors was available in 5,187 individuals, which constitutes the sample examined in the current study. Blood pressure (systolic and diastolic) was measured using a mercury-column sphygmomanometer after 10 min of rest in the supine position. Data on current smoking, diabetes mellitus, and use of antihypertensive and antidiabetic medications was ascertained from a questionnaire. Diabetes mellitus was defined as fasting blood glucose >6.0 mmol/l, self-reported physician diagnosis, or use of antidiabetic medications. MDCS was approved by the Ethics Committee of Lund University, Sweden, and all individuals provided informed consent.

Ascertainment of end points. Cardiac disease end points were ascertained by linkage of Swedish personal identification numbers to the national Swedish registers (Swedish Hospital Discharge Register, Swedish Cause of Death Register) maintained by the Swedish National Board of Health and Welfare. High case validity in these registers has been previously found for heart failure (23), myocardial infarction (24), and atrial fibrillation (25). Heart failure was ascertained from the Swedish Hospital Discharge Register using diagnosis codes 427.00, 427.10, and 428.99 for International Classification of Diseases-8th Revision (ICD-8), 428 for the 9th Revision (ICD-9), and I50 and I11.0 for the 10th Revision (ICD-10) as primary diagnosis as in previous studies (23). Atrial fibrillation was defined using diagnosis codes 427.92 (ICD-8), 427D (ICD-9), and I48 (ICD-10) as in previous studies (25). Myocardial infarction was defined using diagnosis codes 410 (ICD-8 and -9) and I21 (ICD-10) or as death from ischemic heart disease defined using diagnosis codes 412 and 414 (ICD-8 and -9) or I22-I23 and I25 (ICD-10) as in previous studies (24). Follow-up extended to January 1, 2007.

Laboratory measurements. Measurements of fasting blood glucose, HbA1c, insulin, and cholesterol (HDL, triglycerides, total cholesterol) levels were performed in MDC-CC on fresh blood samples according to standard procedures at the Department of Clinical Chemistry, University Hospital Malmö, as described previously (22). Plasma biomarkers were measured from fasting plasma samples that had been frozen at −80°C immediately after collection and that had not previously been thawed (22). Copeptin and the midregional fragments of pro-atrial natriuretic peptide and pro-adrenomedullin were measured using immunoluminometric sandwich assays (BRAHMS, Berlin, Germany). NT-proBNP was measured using the automated Dimension Vista Intelligent Lab System method (Siemens Healthcare Diagnostics Inc., Deerfield, Illinois). CRP was measured by a high-sensitivity assay (Roche Diagnostics, Basel, Switzerland). Cystatin C was measured using a particle-enhanced immuno-nephelometric assay (N Latex Cystatin, Siemens Diagnostics).

Statistical analysis. One individual whose personal identification number did not match national registers was excluded from all analyses, and individuals with prevalent atrial fibrillation or prevalent heart failure were excluded from analyses of the respective disease. MR-proANP, NT-proBNP, CRP, and copeptin showed right-skewed distributions and underwent natural logarithmic transformation. All biomarkers were scaled to an SD of 1 for ease of comparison. Cox proportional hazards models were used to assess association of biomarkers with disease independently of conventional risk factors, with Wald tests for biomarker

significance testing. The proportionality of hazards assumption was confirmed using Schoenfeld's global test. We first assessed association between each disease and each biomarker after adjustment for conventional risk factors. All biomarkers associated with disease ($p < 0.05$) were then included in a backward elimination model with adjustment for conventional risk factors. Performance of the final models was evaluated using the *c*-statistic, a generalization of the area under the receiver-operating characteristic (ROC) curve. Adequate calibration of all final models across quantiles was confirmed using the Grønnesby and Borgan test (26). We tested models for the IDI and for reclassification of individuals into risk categories as the NRI, the proportion of individuals correctly reclassified across risk categories minus the proportion of individuals incorrectly reclassified (20). Finally, we created multimarker risk scores by summing individual *z*-scores weighted by the beta estimate per SD for each biomarker. Kaplan-Meier curves of cumulative incidence were created for comparison of multimarker score quartiles.

The conventional models were determined using regression analysis with backward elimination including age, sex, systolic blood pressure, diastolic blood pressure, use of antihypertensive treatment, body mass index, low-density lipoprotein, high-density lipoprotein, current smoking, history of diabetes mellitus, and history of myocardial infarction. A history of heart failure was also included for atrial fibrillation. For heart failure, we used risk category thresholds of <6%, 6% to <20%, and ≥20% that have been used for coronary heart disease (22,27). For atrial fibrillation, we used risk category thresholds of <5%, 5% to <15%, and ≥15% as proposed for the Framingham prediction model (14).

Secondary analyses were performed with censoring at incident myocardial infarction for heart failure and with censoring at incident myocardial infarction or heart failure for atrial fibrillation. Two-sided p values <0.05 were considered significant. All analyses were performed in SPSS version 16 (SPSS Inc., Chicago, Illinois) or STATA version 8 (StataCorp, College Station, Texas).

Results

Baseline characteristics are shown in Table 1. Atrial fibrillation was prevalent in 47 individuals (0.9%) and heart failure in 8 individuals (0.2%). During a median follow-up of 13.8 years, 112 individuals were diagnosed with new-onset heart failure and 284 individuals were diagnosed with new-onset atrial fibrillation. Of the 63 individuals (1.2%) with both conditions at the end of follow-up, 39 (62%) were diagnosed with atrial fibrillation before heart failure, 15 (24%) were diagnosed with heart failure before atrial fibrillation, and 9 (14%) received both diagnoses on the same day.

Prediction of heart failure and atrial fibrillation with conventional risk factors. Independently significant conventional risk factors used in final models are shown in Table 2 with corresponding hazard ratios. The c-statistic of conventional risk factors was 0.815 for heart failure and 0.732 for atrial fibrillation as shown in Table 3.

Table 1 Baseline Characteristics

Age, yrs	57.6 ± 5.9
Male	2,094 (41)
Systolic blood pressure, mm Hg	141.4 ± 19.0
Diastolic blood pressure, mm Hg	86.9 ± 9.4
Antihypertensive treatment	850 (17)
Body mass index, kg/m^2	25.7 ± 3.9
Low-density lipoprotein, mmol/l	4.2 ± 1.0
High-density lipoprotein, mmol/l	1.4 ± 0.4
Diabetes mellitus	399 (8)
Current smoking	1,379 (27)
History of myocardial infarction	75 (2)
Midregional pro-atrial natriuretic peptide, pmol/l (n = 4,880)	66.1 (50.9–85.9)
N-terminal pro–B-type natriuretic peptide, pg/ml (n = 4,778)	61.0 (34.0–111.0)
Midregional pro-adrenomedullin, nmol/l (n = 4,879)	0.5 ± 0.1
C-reactive protein, mg/l (n = 4,922)	1.4 (0.7–2.8)
Cystatin C, mg/l (n = 4,777)	0.8 ± 0.1
Copeptin, pmol/l (n = 4,873)	5.1 (3.2–8.1)

Shown are baseline characteristics of 5,135 individuals free of atrial fibrillation and heart failure at baseline and with information on all conventional risk factors. For continuous traits, mean ± SD are given for normally distributed traits, and median (interquartile range) for right skewed traits. For categorical traits, n (%) are given.

Biomarkers for prediction of incident heart failure. All biomarkers when considered individually were significantly associated with heart failure after adjustment for conventional risk factors as shown in Table 2. In multivariable regression models with backward elimination including all significant biomarkers and conventional risk factors, NT-proBNP, MR-proANP, and CRP remained significant predictors of heart failure as also shown in Table 2. In secondary analyses with censoring at incident myocardial infarction, NT-proBNP and CRP, but not MR-proANP, remained significant predictors. The pairwise correlation of biomarkers is shown in Online Table 1.

Biomarkers for prediction of incident atrial fibrillation. MR-proANP, NT-proBNP, MR-proADM, and CRP were associated with atrial fibrillation after adjustment for conventional risk factors as shown in Table 2. In multivariable regression models with backward elimination including all significant biomarkers and conventional risk factors, MR-proANP and CRP remained significant as also shown in Table 2. In a secondary analysis with censoring at myocardial infarction or heart failure, both MR-proANP and CRP remained significant predictors independently of conventional risk factors.

Biomarkers and disease discrimination. For heart failure, improvement in discrimination compared with the model with conventional risk factors was observed with inclusion individually of NT-proBNP (*c*-statistic = 0.837), MR-proANP (*c*-statistic = 0.824), or CRP (*c*-statistic = 0.823)

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Table 2 Conventional Risk Factors and Biomarkers for Prediction of Incident HF and AF

	HF Model 1	HF Model 2	AF Model 1	AF Model 2
Age	1.12 (1.07–1.16)	1.09 (1.04–1.13)	1.11 (1.08–1.14)	1.09 (1.06–1.12)
Female sex	0.52 (0.35–0.77)	0.48 (0.31–0.75)	0.61 (0.48–0.78)	0.55 (0.42–0.70)
Body mass index	1.05 (1.00–1.10)	1.03 (0.98–1.09)	1.05 (1.02–1.08)	1.05 (1.01–1.08)
SBP	—	—	1.01 (1.00–1.02)	1.01 (1.00–1.02)
DBP	—	—	0.98 (0.96–1.00)	0.99 (0.98–1.01)
Antihypertensive treatment	2.40 (1.59–3.62)	1.91 (1.20–3.04)	1.38 (1.04–1.84)	1.21 (0.89–1.64)
LDL cholesterol	—	—	1.05 (1.02–1.08)	0.90 (0.78–1.02)
History of MI	4.13 (2.29–7.44)	3.07 (1.64–5.76)	2.64 (1.57–4.44)	1.81 (1.05–3.13)
History of diabetes	2.82 (1.81–4.39)	2.93 (1.82–4.70)	—	—
Current smoking	1.71 (1.13–2.59)	1.56 (0.99–2.46)	—	—
lnMR-proANP	1.68 (1.41–2.00)	1.26 (1.02–1.56)	1.67 (1.47–1.89)	1.62 (1.42–1.84)
lnNT-proBNP	1.95 (1.63–2.34)	1.63 (1.29–2.06)	1.45 (1.28–1.65)	—
MR-proADM	1.35 (1.17–1.56)	—	1.26 (1.12–1.41)	—
lnCRP	1.67 (1.37–2.03)	1.57 (1.28–1.94)	1.17 (1.04–1.33)	1.18 (1.03–1.34)
CystC	1.20 (1.06–1.36)	—	1.11 (1.00–1.24)	—
lnCopeptin	1.35 (1.03–1.77)	—	1.09 (0.95–1.26)	—

Shown are hazards ratios for conventional risk factors and biomarkers per SD with 95% confidence intervals from Cox proportional hazards models. Results are shown for each end point for a model with only conventional risk factors and for single biomarkers with adjustment for conventional risk factors (model 1) and models with all individually significant biomarkers adjusted for traditional risk factors and backward elimination at $p \geq 0.05$ (model 2).

AF = atrial fibrillation; BMI = body mass index; CRP = C-reactive protein; CystC = cystatin C; DBP = diastolic blood pressure; HF = heart failure; LDL = low-density lipoprotein; ln = natural log transformed; MI = myocardial infarction; MR-proADM = midregional pro-adrenomedullin; MR-proANP = midregional pro-atrial natriuretic peptide; NT-proBNP = N-terminal pro–B-type natriuretic peptide; SBP = systolic blood pressure.

in the model as shown in Table 3. Inclusion of all 3 markers together resulted in a *c*-statistic of 0.842.

For atrial fibrillation, improvement in discrimination compared with the model with conventional risk factors was observed with inclusion of MR-proANP (*c*-statistic = 0.750) in the model and, minimally, with CRP (*c*-statistic = 0.734). Inclusion of both biomarkers yielded a *c*-statistic of 0.753.

Biomarkers and risk category reclassification. Net reclassification improvement was observed in 22% of individuals for heart failure with the addition to conventional risk factors of all 3 biomarkers (CRP, MR-proANP, NT-proBNP; NRI $p < 0.001$), mostly due to substantial upward reclassification to a higher risk category (29%) of individuals who were subsequently diagnosed with heart failure during follow-up. For atrial fibrillation, 7% of individuals were reclassified by a model with both biomarkers (CRP, MR-proANP; NRI $p = 0.06$), mostly due to substantial upward reclassification (19%) of individuals who were diagnosed with atrial fibrillation during follow-up to a higher risk category. Multimarker scores yielded similar results with 22% NRI (NRI $p < 0.001$) for heart failure and 6% reclassification (NRI $p = 0.07$) for atrial fibrillation. Results for NRI are shown in Table 3, and numbers reclassified are shown in Table 4. Significant improvement of IDI was also observed for both diseases ($p < 0.001$). The cumulative incidence of heart failure and atrial fibrillation across quartiles of the multimarker risk score is shown in Figure 1. When added to a model with NT-proBNP and conventional risk factors, neither MR-proANP ($p = 0.94$) nor CRP ($p = 0.61$) improved NRI, but improved IDI (MR-proANP: 0.007, $p = 0.02$; CRP: 0.01, $p = 0.005$) for heart failure. The addition of CRP to MR-proANP and conventional risk factors did not improve classification ($p = 0.77$) or IDI ($p = 0.43$) for atrial fibrillation.

Table 3 Discrimination and Risk Category Reclassification Using Biomarkers

	c-Statistic	IDI	NRI
Heart failure			
Conventional risk factors	0.815	—	—
MR-proANP	0.824	0.03 ($p < 0.001$)	14% ($p = 0.005$)
NT-proBNP	0.837	0.03 ($p < 0.001$)	16% ($p = 0.003$)
CRP	0.823	0.01 ($p = 0.02$)	7% ($p = 0.10$)
MR-proANP, NT-proBNP	0.838	0.03 ($p < 0.001$)	17% ($p = 0.002$)
CRP, NT-proBNP	0.842	0.04 ($p < 0.001$)	19% ($p = 0.003$)
All biomarkers	0.842	0.05 ($p < 0.001$)	22% ($p < 0.001$)
Atrial fibrillation			
Conventional risk factors	0.732	—	—
MR-proANP	0.750	0.02 ($p < 0.001$)	8% ($p = 0.04$)
CRP	0.734	0.001 ($p = 0.25$)	2% ($p = 0.32$)
Both	0.753	0.02 ($p < 0.001$)	7% ($p = 0.06$)

Shown are measures of discrimination and reclassification for models with conventional risk factors only and models with the addition of biomarkers to conventional risk factors for heart failure (HF) and atrial fibrillation (AF). For IDI, the IDI statistics and p values are shown. For NRI, the proportion of individuals correctly reclassified minus the proportion of individuals incorrectly reclassified and p values are shown.

Abbreviations as in Table 2.

Discussion

In this community-based cohort, we found that conventional cardiovascular risk factors predicted heart failure and atrial fibrillation with reasonable accuracy and that the addition of biomarkers to conventional risk factors modestly

Table 4 Risk Classification by Models With and Without Biomarkers for HF or AF

Model With Conventional Risk Factors	Model With Biomarkers			
	Category 1	Category 2	Category 3	Total
Heart failure				
Category 1 (<6%)	44/4,274	14/108	3/7	61/4,389
Category 2 (6% to <20%)	5/124	9/124	11/30	25/278
Category 3 (≥20%)	0/0	2/12	8/25	10/37
Total	49/4,398	25/244	22/62	96/4,704
Atrial fibrillation				
Category 1 (<5%)	57/2,640	15/221	0/0	72/2,861
Category 2 (5% to <15%)	24/388	92/1,228	34/137	150/1,753
Category 3 (≥15%)	0/0	13/64	21/105	34/169
Total	81/3,028	120/1,513	55/242	256/4,783

Reclassification across risk groups defined as <6%, 6% to <20%, ≥20% for heart failure (HF) and defined as <5%, 5% to 15%, ≥15% for atrial fibrillation (AF). Numbers in the cells refer to numbers of observed events during follow-up over the total number of individuals in each combination of categories.

improved discrimination for both diseases and substantially improved risk classification for heart failure. This improvement was mainly mediated by natriuretic peptides. These findings stand in contrast to the weaker performance of contemporary cardiovascular biomarkers (such as CRP and BNP) in improving discrimination and risk category classification for atherosclerotic events above conventional risk factors in the general population (22,28,29). One potential explanation for this difference could be a smaller value of conventional risk factors for prediction of heart failure and atrial fibrillation, compared with atherosclerotic events, providing greater room for improvement with biomarkers. Indeed, the population-attributable risk for conventional risk factors for myocardial infarction (30) has been described to be substantially higher than for heart failure (10,31) and atrial fibrillation (11). Still, we observed excellent discrimination of heart failure using conventional risk factors (*c*-statistic = 0.815) and acceptable discrimination of atrial fibrillation (*c*-statistic = 0.753). Our models with conventional risk factors contained fewer risk factors and had similar or better predictive accuracy to that described for previous models for both AF and HF (14,15).

Findings and implications for HF. Prior studies have noted the association of CRP and natriuretic peptides with future heart failure (16), but there has been limited information regarding the additive value of these biomarkers for risk prediction. Furthermore, prior studies have frequently included fewer than 100 heart failure events. Thus, the present investigation extends the findings of prior studies to a larger cohort, with the use of novel predictive indexes and assessment of a large panel of contemporary biomarkers.

Our data suggest that the association between NT-proBNP, MR-proANP, and CRP with heart failure risk is not mediated by interim myocardial infarction. Mild natriuretic peptide elevation may reflect asymptomatic left ventricular systolic or diastolic dysfunction (32,33). Asymptomatic left ventricular dysfunction is common in the population (32), and can progress to heart failure over time (34,35). Although we did not have concurrent echocardiographic measures, it is interesting to note that prior investigations have found the association of BNP with incident heart failure to be independent of left ventricular mass, ejection fraction, or left atrial enlargement, suggesting that natriuretic peptide elevations may reflect more subtle cardiac abnormalities. The association of CRP with heart failure has been postulated to reflect active inflammatory processes in the myocardium which, following an initial precipitating

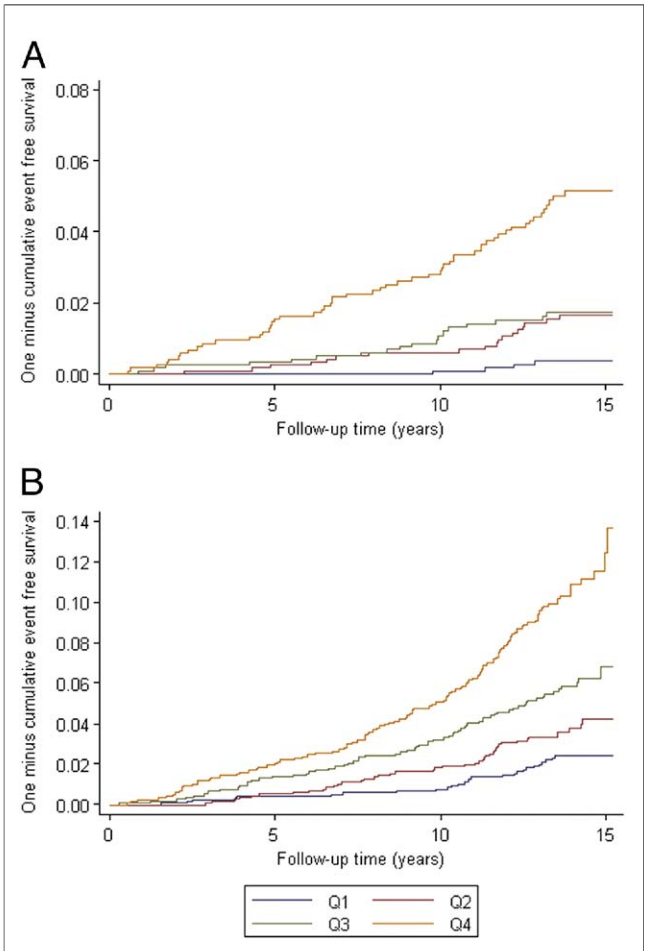

Figure 1 Cumulative Incidence of HF and AF

Panels show the cumulative incidence of **(A)** heart failure (HF) and **(B)** atrial fibrillation (AF) during follow-up across quartiles of multimarker scores. Individuals in **A** were free of HF at baseline, and individuals in **B** were free of AF at baseline. Risk score distribution expressed as median (minimum, maximum) for HF was −3.4 (−11.2, −2.0) for the first quartile (Q1), −1.0 (−2.0, −0.6) for the second quartile (Q2), 0.8 (−0.6, 1.9) for the third quartile (Q3), and 3.3 (1.9, 13.2) for the fourth quartile (Q4). Risk score distribution for AF was −2.2 (−12.7, −1.3) for the first quartile, −0.7 (−1.3, −0.3) for the second quartile, 0.5 (−0.3, 1.2) for the third quartile, and 2.2 (1.2, 11.2) for the fourth quartile. p values for trend were <0.001 for both HF and AF.

event, progressively drive remodeling and dilation of cardiac chambers (16,18). However, further data are warranted to establish the underlying mechanisms, and the improvement in discrimination with CRP was modest. It is possible that better markers reflecting myocardial remodeling and other pathways exist and will improve risk prediction beyond natriuretic peptides.

Improved ability to identify individuals at risk for heart failure could be useful to identify individuals who might benefit from echocardiographic testing and to guide preventive interventions such as angiotensin-converting enzyme inhibitors, which have been found to prevent the development of heart failure and improve survival in individuals with asymptomatic left ventricular dysfunction (34,36). Further studies are necessary to determine whether any subgroups might benefit more from biomarker testing, what the appropriate follow-up of positive biomarker results should be (e.g., echocardiography), and the cost effectiveness of more widespread screening (37,38).

Findings and implications for atrial fibrillation. Natriuretic peptides and inflammation were also the best markers for atrial fibrillation. Our data suggest that these associations are not mediated by interim myocardial infarction and heart failure. Interestingly, MR-proANP performed slightly better than NT-proBNP, suggesting that the former could be a better marker of the atrial stress leading to atrial fibrillation. This finding is supported by the observation in the Framingham Heart Study that N-terminal pro-atrial natriuretic peptide levels predicted atrial fibrillation more strongly than NT-proBNP (17). CRP predicted atrial fibrillation with similar risk estimates as in a previous study (18). However, CRP, a relatively weak predictor on its own with only minimal improvement in discrimination, did not substantially improve prediction when added to MR-proANP.

Unfortunately, no preventive treatments for atrial fibrillation have been established. Subgroup analyses of clinical trials have shown interesting results with angiotensin receptor inhibitors, statins, and beta-blockers, and calls for additional trials to address this issue have been raised, but the current data are inconclusive (8).

Study strengths and limitations. We used a large sample with long follow-up, enabling identification of large numbers of disease events. Our use of national register data could potentially reduce the impact of attendance bias on end point ascertainment, which could be substantial for heart failure. High case validity of atrial fibrillation, heart failure, and myocardial infarction has been validated in these registers (23–25). However, as disease outcomes were ascertained from national registers on cause of death and hospitalization, it is possible that individuals who developed disease but were not hospitalized escaped detection, leading to underestimates of disease rates. It seems less likely that these effects would be differential based on the biomarkers measured here and thus would be more likely to bias our study to the null.

Conclusions

Our findings provide evidence that natriuretic peptides improve prediction of incident heart failure and atrial fibrillation in the general population in addition to conventional risk factors. Whether individuals with elevated levels of these biomarkers will benefit from further testing and preventive therapy remains to be determined.

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Key Words: atrial fibrillation ■ epidemiology ■ heart failure ■ natriuretic peptides ■ prediction ■ risk factors.

APPENDIX

For a supplementary table, please see the online version of this article.